

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 285/14, A61K 31/445, C07D 271/12, 413/06, A61K 31/535, C07D 417/06, A61K 31/54, C07D 498/10</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/35950 (43) International Publication Date: 20 August 1998 (20.08.98)</p>
<p>(21) International Application Number: PCT/US98/02713 (22) International Filing Date: 13 February 1998 (13.02.98) (30) Priority Data: 08/800,108 13 February 1997 (13.02.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/800,108 (CIP) Filed on 13 February 1997 (13.02.97) (71) Applicant (for all designated States except US): CORTEX PHARMACEUTICALS, INC. [US/US]; 15241 Barranca Parkway, Irvine, CA 92718 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ROGERS, Gary, A. [US/US]; 3056 Foothill Road, Santa Barbara, CA 93105 (US). MARRS, Christopher, M. [US/US]; 2 Parterre Avenue, Foothill Ranch, CA 92610 (US). (74) Agents: GORTHEY, LeeAnn et al.; Dehlinger & Associates, LLP, P.O. Box 60850, Palo Alto, CA 94306-0850 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: BENZOFURAZAN COMPOUNDS WHICH ENHANCE AMPA RECEPTOR ACTIVITY</p> <p>(57) Abstract</p> <p>Compounds of general structural formula (I) are shown to have AMPA receptor enhancing properties. The compounds are useful for such therapeutic purposes as facilitating the learning of behaviors dependent upon AMPA receptors, and in treating conditions, such as memory impairment, in which AMPA receptors, or synapses utilizing these receptors, are reduced in numbers or efficiency. They may also be used to enhance excitatory synaptic activity in order to restore an imbalance between brain subregions, as in treatment of schizophrenia or schizophreniform behavior.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

BENZOFURAZAN COMPOUNDS WHICH ENHANCE AMPA RECEPTOR ACTIVITY

Field of the Invention

5 This invention relates to the prevention and treatment of cerebral insufficiency, including enhancement of receptor functioning in synapses in brain networks responsible for higher order behaviors. These brain networks are involved in cognitive abilities related to memory impairment, such as is observed in a variety of dementias, and in imbalances in neuronal activity between different brain regions, as is suggested in disorders such as
10 schizophrenia. In a particular aspect, the invention relates to compounds useful for treatment of such conditions, and methods of using these compounds for such treatment.

Background of the Invention

 The release of glutamate at synapses at many sites in mammalian forebrain
15 stimulates two classes of postsynaptic receptors. These classes are usually referred to as AMPA/quisqualate and N-methyl-D-aspartic acid (NMDA) receptors. AMPA/quisqualate receptors mediate a voltage independent fast excitatory post-synaptic current (the fast EPSC), whereas NMDA receptors generate a voltage-dependent, slow excitatory current. Studies carried out in slices of hippocampus or cortex indicate that the AMPA receptor
20 mediated fast EPSC is generally the dominant component by far at most glutamatergic synapses.

 AMPA receptors are not evenly distributed across the brain but rather are largely restricted to telencephalon and cerebellum. These receptors are found in high concentrations in the superficial layers of neocortex, in each of the major synaptic zones of
25 hippocampus, and in the striatal complex, as reported by Monaghan *et al.* in *Brain Research* 324:160-164 (1984). Studies in animals and humans indicate that these structures organize complex perceptual-motor processes and provide the substrates for higher-order behaviors. Thus, AMPA receptors mediate transmission in those brain networks responsible for a host of cognitive activities.

30 For these reasons, drugs that enhance the functioning of AMPA receptors could have significant benefits for intellectual performance. Such drugs should also facilitate memory encoding. Experimental studies, such as those reported by Arai and Lynch, *Brain Research* 598:173-184 (1992), indicate that increasing the size of AMPA receptor-mediated synaptic response(s) enhances the induction of long-term potentiation

(LTP). LTP is a stable increase in the strength of synaptic contacts that follows repetitive physiological activity of a type known to occur in the brain during learning.

Compounds that enhance the functioning of the AMPA form of glutamate receptors facilitate the induction of LTP and the acquisition of learned tasks, as measured by a number of paradigms. See, for example, Granger *et al.*, *Synapse* 15:326-329 (1993); Staubli *et al.*, *PNAS* 91:777-781 (1994); Arai *et al.*, *Brain Res.* 638:343-346 (1994); Staubli *et al.*, *PNAS* 91:11158-11162 (1994); Shors *et al.*, *Neurosci. Let.* 186:153-156 (1995); Larson *et al.*, *J. Neurosci.* 15:8023-8030 (1995); Granger *et al.*, *Synapse* 22:332-337 (1996); Arai *et al.*, *JPET* 278:627-638 (1996); Lynch *et al.*, *Internat. Clin. Psychopharm.* 11:13-19 (1996); and Lynch and Rogers, PCT Pubn. No. WO 94/02475. There is a considerable body of evidence showing that LTP is the substrate of memory. For example, compounds that block LTP interfere with memory formation in animals, and certain drugs that disrupt learning in humans antagonize the stabilization of LTP, as reported by del Cerro and Lynch, *Neuroscience* 49:1-6 (1992).

A possible prototype for a compound that selectively facilitates the AMPA receptor has been described by Ito *et al.*, *J. Physiol.* 424:533-543 (1990). These authors found that the nootropic drug aniracetam (N-anisoyl-2-pyrrolidinone) increases currents mediated by brain AMPA receptors expressed in *Xenopus* oocytes without affecting responses by gamma-aminobutyric acid (GABA), kainic acid (KA), or NMDA receptors. Infusion of aniracetam into slices of hippocampus was also shown to increase the size of fast synaptic potentials without altering resting membrane properties. It has since been confirmed that aniracetam enhances synaptic responses at several sites in hippocampus, and that it has no effect on NMDA-receptor mediated potentials. See, for example, Staubli *et al.*, *Psychobiology* 18:377-381 (1990) and Xiao *et al.*, *Hippocampus* 1:373-380 (1991).

Aniracetam has been found to have a rapid onset and washout, and can be applied repeatedly with no apparent lasting effects, which are desirable features for behaviorally relevant drugs. Aniracetam does present several disadvantages, however. The peripheral administration of aniracetam is not likely to influence brain receptors. The drug works only at high concentrations (approx. 1.0 mM), and about 80% of the drug is converted to anisoyl-GABA following peripheral administration in humans (Guenzi and Zanetti, *J. Chromatogr.* 530:397-406 (1990)). The metabolite, anisoyl-GABA, has been found to have less activity than aniracetam.

A class of AMPA receptor-enhancing compounds that does not display the low potency and inherent instability characteristics of aniracetam has been described (Lynch and Rogers, PCT Pubn. No. WO 94/02475). These compounds, termed "AMPAKINES"TM, are substituted benzamides which include, for example, 1-(1,3-benzodioxol-5-ylcarbonyl)piperidine. They are chemically more stable than aniracetam and show improved bioavailability as judged by experiments performed by Positron Emission Tomography (PET) (see, for example, Staubli *et al.*, in *PNAS* 91:11158-11162 (1994)).

Another class of Ampakines, benzoxazines, has been discovered recently to have very high activity in *in vitro* and *in vivo* models for assessing the probability of producing cognition enhancement, as described in PCT Pubn. No. WO 97/36907, "Benzoxazines for Enhancing Synaptic Response", by Rogers and Lynch. Some, but not all, of these compounds show activity in a rat model for the human disease, schizophrenia (Larson *et al.*, *Brain Res.* 728: 353-356 (1996)).

Certain substituted benzofurazan and benzothiadiazole compounds have been found to be significantly and surprisingly more potent in the animal model of schizophrenia than these previously reported compounds, and are also effective in cognition enhancement. These compounds are disclosed herein.

Summary of the Invention

The present invention includes, in one aspect, compounds as shown and described in Section II of the Detailed Description, following. The compounds are effective to increase AMPA receptor-mediated responses and are thus useful for a variety of purposes. These include facilitating the learning of behaviors dependent upon AMPA receptors, treating conditions in which AMPA receptors, or synapses utilizing these receptors, are reduced in numbers or efficiency, and enhancing excitatory synaptic activity in order to restore an imbalance between brain subregions. The invention thereby provides a method for the treatment of a mammalian subject suffering from a hypoglutamatergic condition, or from a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors, such that memory or other cognitive functions are impaired. Such conditions may also cause a cortical/striatal imbalance, leading to schizophrenia or schizophreniform behavior.

According to the method, the subject is treated with an effective amount of a compound as shown and described in Section II of the Detailed Description, following, in a pharmaceutically acceptable carrier. As demonstrated below, the compounds are significantly more potent than previously described compounds in increasing AMPA receptor function in slices of rat hippocampus, in animal models of schizophrenia and depression, and in enhancing cognitive performance, such as performance in an 8-arm radial maze.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

10

Brief Description of the Drawings

Figure 1 shows a method of preparing a preferred compound of the invention;

Figures 2A-2D show methods of preparing tetracyclic compounds that form one embodiment of the invention; and

Figure 3 represents a selection of compounds useful in practicing the method of the invention.

Detailed Description of the Invention

I. Definitions

The terms below have the following meanings unless indicated otherwise.

"Alkyl" refers to a fully saturated monovalent radical containing carbon and hydrogen, and which may be cyclic, branched or a straight chain. Examples of alkyl groups are methyl, ethyl, n-butyl, n-heptyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl, and cyclohexyl.

"Aryl" refers to a substituted or unsubstituted monovalent aromatic radical having a single ring (*e.g.*, benzene) or multiple condensed rings (*e.g.*, naphthyl). Other examples include heterocyclic aromatic ring systems having one or more nitrogen, oxygen, or sulfur atoms in the ring, such as imidazole, furyl, pyrrole, pyridyl, and indole.

The term "effective amount" refers to the amount of a selected compound of formula I which is necessary to enhance glutamatergic synaptic response by increasing AMPA receptor activity. The precise amount required will vary depending upon the particular compound selected, the age and weight of the subject, route of administration,

and so forth, but may be easily determined by routine experimentation.

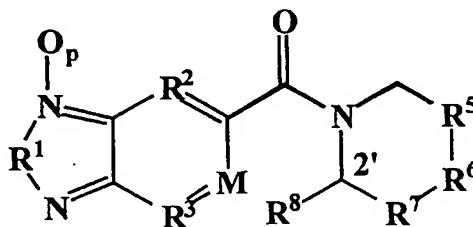
The term "pharmaceutically acceptable carrier" refers to a carrier or excipient which is not unacceptably toxic to the subject to which it is administered. Pharmaceutically acceptable excipients are described at length by E.W. Martin, in "Remington's

5 Pharmaceutical Sciences."

II. AMPA Receptor Enhancing Compounds

The present invention is directed, in one aspect, to compounds having AMPA receptor enhancing properties. These are compounds having the structure I, below:

10



in which:

R¹ is oxygen or sulfur;

15 R² and R³ are independently selected from the group consisting of -N=, -CR=, and -CX=;

M is =N- or =CR⁴-, wherein R⁴ and R⁸ are independently R or together form a single linking moiety linking M to the ring vertex 2', the linking moiety being selected from the group consisting of a single bond, -CRR'-, -CR=CR'-, -C(O)-, -O-, -S(O)_y-,

20 -NR-, and -N=; and

R⁵ and R⁷ are independently selected from the group consisting of -(CRR')_n-, -C(O)-, -CR=CR'-, -CR=CX-, -CRX-, -CXX'-, -S-, and -O-, and

R⁶ is selected from the group consisting of -(CRR')_m-, -C(O)-, -CR=CR'-, -CRX-, -CXX'-, -S-, and -O-;

25 wherein

X and X' are independently selected from -Br, -Cl, -F, -CN, -NO₂, -OR, -SR, -NRR', -C(O)R, -CO₂R, or -CONRR', where two R or R' groups on individual or separate X groups may together form a ring;

R and R' are independently selected from (i) hydrogen, (ii) C₁-C₆ branched or unbranched alkyl, which may be unsubstituted or substituted with one or more functionalities selected from halogen, nitro, alkoxy, hydroxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide, and where two such alkyl groups on a single carbon or on adjacent carbons may together form a ring, and (iii) aryl, which may be unsubstituted or substituted with one or more functionalities selected from halogen, nitro, alkoxy, hydroxy, aryloxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide;

m and p are, independently, 0 or 1; and

10 n and y are, independently, 0, 1 or 2.

Preferred subsets of the compounds encompassed by formula I include those in which p is 0, those in which R² and R³ are -CR= and M is =CR⁴, particularly where R⁴ is hydrogen, and those in which R¹ is oxygen. A particularly preferred subset is one in which all of the above qualifications apply, and more preferably in which R⁵ and R⁷ are - (CRR')_n- and R⁶ is -(CRR')_m-; that is, certain 5-carboxamido benzofurazan derivatives containing different-sized saturated heterocyclic rings linked to the carbonyl group.

Preferred compounds of this subset are those in which R and R' are selected from (i) hydrogen or (ii) alkyl, as defined above. A particularly preferred compound of this group is 1-(benzofurazan-5-ylcarbonyl)piperidine, designated herein as compound 2. Also preferred is the corresponding compound in which R¹ is sulfur; that is, 1-(benzo-2,1,3-thiadiazole-5-ylcarbonyl)piperidine, designated herein as compound 1. Other examples, having differently sized rings (where n is 1 and m is 0 or 2, respectively) include 1-(benzofurazan-5-ylcarbonyl)pyrrolidine (11) and 1-(benzofurazan-5-ylcarbonyl)hexamethyleneimine (14).

25 A second preferred subset of the compounds of formula I is that in which p is 0, R⁴ and R⁸ are both hydrogen, R⁶ is -(CRR')_m-, R⁷ is -(CRR')_n-, and R⁵ is -CR=CX- or -CR=CR'-, that is, the heterocyclic ring includes a double bond. A further preferred class of this second subset is that in which m is 0. Particularly preferred examples of this class are those compounds in which R¹ is oxygen, n is 1, and R and R' are hydrogen, that is, 1-(benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine, designated herein as compound 3, and 1-(benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydro-4-fluoropyridine, designated herein as compound 6. A further example, having a 5-membered ring (m and n are both zero), is

1-(benzofurazan-5-ylcarbonyl)-pyrroline (12).

A third preferred subset of formula I includes those compounds in which p is 0, R¹ is oxygen, R⁴ and R⁸ are both hydrogen, R⁵ and R⁷ are -(CRR')_n-, and R⁶ is -C(O)-, -CRX-, CXX'-, -O-, or -S-. A further preferred class of this third subset is that in which
 5 R⁶ is -CRX- or -CXX'-, where R and X are each selected from the groups defined above, and n is 1. Two particularly preferred examples of this class are 1-(benzofurazan-5-ylcarbonyl)-4'-cyanopiperidine (compound 8) and 1-(benzofurazan-5-ylcarbonyl)-4'-hydroxypiperidine (compound 9). Also preferred are those in which X is fluorine and R and R' are hydrogen; that is, 1-(benzofurazan-5-ylcarbonyl)-4'-fluoropiperidine and
 10 1-(benzofurazan-5-ylcarbonyl)-4',4'-difluoropiperidine, designated herein as compounds 4 and 5, respectively. Other examples include the corresponding 4-methylpiperidine and 4-methoxypiperidine derivatives (13 and 17, respectively).

When any of R⁵, R⁶, and R⁷ is CXX', two groups X and X' on the same or adjacent carbons may form a ring, as noted above. An example is 1-(benzofurazan-5-ylcarbonyl)-
 15 1,4-dioxo-8-azaspiro[4,5]decane (15).

Another preferred class of this third subset is that in which n is 1, R and R' are hydrogen, and R⁶ is oxygen or sulfur. This class includes morpholino and thiomorpholino amides of benzofurazan, *i.e.* N-(benzofurazan-5-ylcarbonyl)morpholine (7) and N-(benzofurazan-5-ylcarbonyl)thiomorpholine (10). In compound 16, derived from 4-pyridinone,
 20 R⁶ is -C(O)-.

A fourth preferred subset of the compounds of formula I is that in which M is =CR⁴-, where R⁴ and R⁸ together form a single linking moiety linking M to the ring vertex 2'. This linking moiety is selected from the group consisting of a single bond, -CRR'-, -CR=CR'-, -C(O)-, -O-, -S-, -NR-, and -N=. Preferred compounds of this fourth subset
 25 include those in which p is 0, those in which R¹ is oxygen, and those in which R² and R³ are -CR=, where R is defined as above. Particularly preferred compounds are those in which all of the above qualifications apply; that is, certain tetracyclic benzofurazan amides, such as those represented in Fig. 2. A preferred group of these compounds includes those in which the linking moiety is selected from -CRR'-, -O-, -S-, and -N=.

30 Preferably, R⁵ and R⁷ are -(CRR')_n-, and R⁶ is -(CRR')_m-. More preferably, in this case, n is 1, and m is 0 or 1, giving a 5-membered or 6-membered heterocyclic ring, respectively, as the rightmost fused ring. Of the preferred linking moieties, -CRR'-, oxygen, sulfur,

and -N=, oxygen and imino (-N=) are particularly preferred, with oxygen being most preferred.

III. Preparation of Subject Compounds

5 The compounds of the present invention can be synthesized in a variety of ways, using conventional synthetic chemistry techniques. Methods for the preparation of the compounds of the present invention include the following.

 Compounds of the invention in which R⁴ and R⁸ do not form a linking moiety are conveniently prepared, as shown in Fig. 1, by activation of the carboxyl group of an
10 appropriately substituted benzoic acid, or, alternatively, a nicotinic, pyrazinoic, pyridizine carboxylic, or pyrimidine carboxylic acid, with carbonyldiimidazole or another activating group, e.g. thionyl chloride, in an anhydrous solvent such as dichloromethane, chloroform, tetrahydrofuran, or ethyl acetate. A cyclic amine is then reacted with the
15 activated carboxyl group. The cyclic amine preferably includes, in accordance with the preferred structures described above, an optionally substituted piperidine derivative. The ring may also include unsaturation or an oxygen or sulfur ring atom, and larger or smaller ring sizes are also contemplated. A large selection of such amines is commercially available; alternatively, they may be prepared using well established synthetic methods.

 Examples 1-20 describe preparation of representative compounds of the invention,
20 designated herein as compounds 1 to 18, according to the methods described above.

 Compounds of the invention in which R⁴ and R⁸ form a linking moiety may be prepared according to methods such as those shown in Figs 2A-2D. Although the illustrated preparations employ a benzofurazan nucleus, similar methods may be used to prepare other compounds of the invention, *e.g.* the corresponding benzothiadiazoles and
25 other nitrogen-containing heteroaromatic systems.

 As shown in Fig. 2A, activation of the carboxyl group of an appropriately substituted salicylic acid with carbonyldiimidazole, in an anhydrous solvent such as dichloromethane, chloroform, tetrahydrofuran, ethyl acetate, or the like, is followed by addition of a suitable aminoalkylacetal. The resulting amide acetal is treated with a strong
30 acid, such as an alkyl or aryl sulfonic acid, or trifluoroacetic acid in a solvent of low basicity, such as dichloromethane, to effect cleavage of the acetal and cyclization to a tetracyclic substituted benzoxazine, as shown, in which the linking moiety formed by R⁴

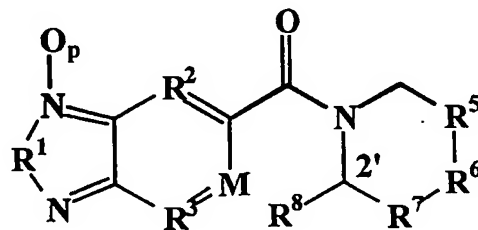
and R⁸ is oxygen. An alternative method of preparation, shown in Fig. 2B, reacts the activated salicylate with a cyclic imine, such as 1-pyrroline or 2,3,4,5-tetrahydropyridine.

Fig. 2C shows the reaction of a suitably substituted anthranilate ester with a cyclic haloimine, such as a 2-chloro- or 2-bromoimidate, to yield a tetracyclic compound in which the linking moiety formed by R⁴ and R⁸ is an imino group. This group may be subsequently reduced by, for example, catalytic hydrogenation, to give an amino linking moiety.

Fig. 2D shows the reaction of a suitably substituted homophthalic anhydride with a cyclic imine, such as 1-pyrroline or 2,3,4,5-tetrahydropyridine, followed by decarboxylation, to yield a tetracyclic compound in which the linking moiety formed by R⁴ and R⁸ is a -CH₂- or -CRR'- group. (See, for example, Cushman *et al.*, *J. Org. Chem.* 45:5067-5073 (1980), and Smith *et al.*, *J. Heterocyclic Chem.* 28:1813-1815 (1991).)

IV. Method of Treatment

According to a further aspect of the invention, the subject compositions are useful for the treatment of schizophrenia or schizophreniform behavior in a mammalian subject, or for treating impairment in memory or other cognitive functions. Such maladies are symptomatic of a hypoglutamatergic condition, or of deficiencies in the number or strength of excitatory synapses, or in the number of AMPA receptors. Because treatment of a subject with the subject compositions enhances AMPA receptor activity, such treatment may also be used to facilitate the learning of behaviors dependent upon AMPA receptors. The method of treatment comprises administering to the subject, in a pharmaceutically acceptable carrier, an effective amount of a compound having the formula:



wherein

R¹ is oxygen or sulfur;

R² and R³ are independently selected from the group consisting of -N=, -CR=, and -CX=;

M is =N- or =CR⁴-, wherein R⁴ and R⁸ are independently R or together form a single linking moiety linking M to the ring vertex 2', the linking moiety being selected from the group consisting of a single bond, -CRR'-, -CR=CR'-, C(O)-, -O-, -S(O)_y-, -NR-, and -N=;

- 5 R⁵ and R⁷ are independently selected from the group consisting of -(CRR')_n-, -C(O)-, -CR=CR'-, -CR=CX-, -CRX-, -CXX'-, -S-, and -O-, and R⁶ is selected from the group consisting of -(CRR')_m-, -C(O)-, -CR=CR'-, -CRX-, -CXX'-, -S-, and -O-; wherein

- 10 X and X' are independently selected from -Br, -Cl, -F, -CN, -NO₂, -OR, -SR, -NRR', -C(O)R, -CO₂R, or -CONRR', wherein two groups R or R' on an individual group X, or on two adjacent groups X, may together form a ring; and and

- R and R' are independently selected from (i) hydrogen, (ii) C₁-C₆ branched or unbranched alkyl, which may be unsubstituted or substituted with one or more
15 functionalities selected from halogen, nitro, alkoxy, hydroxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide, and wherein two such alkyl groups on a single carbon or on adjacent carbons may together form a ring, and (iii) aryl, which may be unsubstituted or substituted with one or more functionalities selected from halogen, nitro, alkoxy, hydroxy, aryloxy, alkylthio, amino, keto, aldehyde,
20 carboxylic acid, carboxylic ester, or carboxylic amide;

m and p are, independently, 0 or 1; and

n and y are, independently, 0, 1 or 2.

- Of the compounds administered according to the method, preferred groups include those described in Section II, above. Particularly preferred are those compounds
25 designated as compounds 1 through 9, with compounds 2, 7, 8 and 9 being most preferred.

The compounds administered in accordance with the method have been found to be more effective than previously described compounds in enhancing AMPA receptor activity, as shown in the *in vitro* and *in vivo* tests described below.

30 V. Biological Activity

A. Enhancement of AMPA Receptor Function

Synaptic responses mediated by AMPA receptors are increased according to the

method of the invention, using the compounds described herein. These compounds are demonstrated, in the Examples that follow, to be substantially more potent than previously-described compounds in increasing AMPA receptor function in slices of rat hippocampus. This *in vitro* assay is described as follows, and in Example 21, below.

5 The field EPSP (excitatory post-synaptic potential) recorded in field CA1 after stimulation of CA3 axons is known to be mediated by AMPA receptors, which are present in the synapses (Kessler *et al.*, *Brain Res.* 560: 337-341 (1991)). Drugs that selectively block the receptor selectively block the field EPSP (Muller *et al.*, *Science*, *supra*). Aniracetam, which has been shown to increase the mean open time of the AMPA receptor channel,
10 increases the amplitude of the synaptic current and prolongs its duration (Tang *et al.*, *Science*, *supra*). These effects are mirrored in the field EPSP (see, for example, Staubli *et al.*, *Psychobiology*, *supra*; Xiao *et al.*, *Hippocampus*, *supra*; Staubli *et al.*, *Hippocampus* 2: 4958 (1992)). Similar results have been reported for the previously disclosed stable benzamide analogs of aniracetam (Lynch and Rogers, PCT Pubn. No. WO 94/02475).

15 To obtain the data shown in Table I, a bipolar nichrome stimulating electrode was positioned in the dendritic layer (stratum radiatum) of the hippocampal subfield CA1 close to the border of subfield CA3, as described in Example 21. Current pulses (0.1 msec) through the stimulating electrode activate a population of the Schaffer-commissural (SC) fibers, which arise from neurons in the subdivision CA3 and terminate in synapses on the
20 dendrites of CA1 neurons. Activation of these synapses causes them to release the transmitter glutamate. Glutamate binds to the post-synaptic AMPA receptors which then transiently open an associated ion channel and permit a sodium current to enter the post-synaptic cell. This current results in a voltage in the extracellular space (the field EPSP), which is recorded by a high impedance recording electrode positioned in the middle of the
25 stratum radiatum of CA1.

The intensity of the stimulation current was adjusted to produce half-maximal EPSPs (typically about 1.5 - 2.0 mV). Paired stimulation pulses were given every 40 sec with an interpulse interval of 200 msec, as described further in Example 21.

Hippocampal slices were maintained in a recording chamber continuously perfused
30 with artificial cerebrospinal fluid (ACSF). During 15 - 30 minute intervals, the perfusion medium was switched to one containing various concentrations of the test compounds. Responses collected immediately before and at the end of drug perfusion were

superimposed in order to calculate the percent increase in EPSP amplitude.

Invention compounds 1 – 9, as shown in Fig. 3 and Table I below, and reference compound CX516 (1-(quinoxalin-6-ylcarbonyl)piperidine), disclosed in PCT Pubn. No. WO 94/02475, were assayed in the physiological test system described above. The first data column of Table 1 shows the estimate of the concentration of each test compound that would be required to increase the amplitude of the field EPSP to a value 10% above the baseline level.

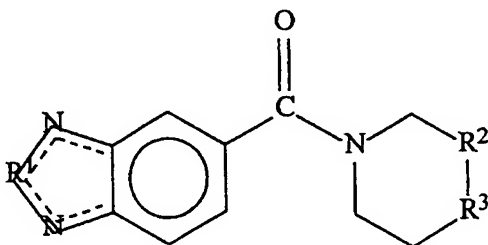


Table I

Compound #	R ¹	R ²	R ³	Amp ¹ (μM)	MED _s ² (mg/kg)	MED _c ³ (mg/kg)	MED _d ⁴ (mg/kg)
CX516	CHCH	CH ₂	CH ₂	50	10	15	5
1	S	CH ₂	CH ₂	< 100	NT	NT	NT
2	O	CH ₂	CH ₂	3	0.1	0.1	0.01
3	O	CH	CH	100	NT	NT	NT
4	O	CH ₂	CHF	30	1	NT	NT
5	O	CH ₂	CF ₂	50	1	NT	NT
6	O	CH	CF	30	NT	NT	NT
7	O	CH ₂	O	3	ND	0.1	NT
8	O	CH ₂	CHCN	1	ND	0.1	NT
9	O	CH ₂	CHOH	20	ND	0.1	0.01

20

¹Concentration of compound that causes a 10% increase in the amplitude of the field EPSP in Field CA1 of rat hippocampal slice.

25

²Minimum Effective Dose that produces a statistically significant improvement in behavior in the animal model of schizophrenia.

³Minimum Effective Dose that produces a statistically significant improvement in behavior in the eight-arm radial maze task for cognition/memory enhancement.

30

⁴Minimum Effective Dose that produces a statistically significant improvement in behavior in an animal model of depression.

NT = Not tested; ND = Not determined

As the data in Table 1 show, the present compounds produced a dose-dependent increase in the amplitude of the EPSP and were effective at concentrations as low as 3 μ M. The majority of the tested compounds were equally or more effective, up to a factor of about fifty, than the reference compound, CX516, in increasing AMPA receptor function.

5 Compounds 2, 4, and 6 – 9 were particularly effective.

Studies that compared the effects of AMPA modulators on monosynaptic (as reported here) and polysynaptic responses demonstrated that a 10% increase in the amplitude of the monosynaptic field EPSP was amplified to an increase of 300% on a trisynaptic response (Servio *et al.*, *Neuroscience* 74: 1025-1035 (1996)). Furthermore, the
10 concentration of the modulator that evoked these responses was shown to exist in plasma from behaviorally relevant doses (Granger *et al.*, *Synapse*, *supra*). Thus, a 10% increase in amplitude of the monosynaptic field EPSP, as reported in the table, is likely to represent a behaviorally relevant plasma concentration.

B. Behavioral Testing

15 The compounds of the invention are also effective in relevant animal models of disease, such as schizophrenia and depression, and in models of cognitive performance, such as performance in an 8-arm radial maze.

The second data column in Table 1 shows the Minimum Effective Dose (MED₅) for efficacy in the methamphetamine/rat model, which has proven useful in assessing the
20 efficacy of neuroleptic drugs for the treatment of schizophrenia (Larson *et al.*, *Brain Res.*, *supra*). The dose recorded is that which reduced the hyperactivity and/or the stereotypic activity induced by acute administration of 2 mg/kg methamphetamine in rats, as described in Example 22.

All of the compounds tested were significantly more effective than the reference
25 compound, as shown in the Table, in that a ten-fold or greater reduction in dose produced an equivalent effect. Compound 2 was equally effective at a hundred-fold reduction in dose.

The third data column shows the MED for efficacy to improve performance in the eight-arm radial maze task, which tests for improved memory and cognition (MED_C).
30 This task has been described previously (Staubli *et al.*, *PNAS* 91:777-781 (1994)) and Lynch and Rogers, PCT Pubn. No. WO 94/02475). Again, all of the tested compounds (2 and 7 – 9) were several times more potent than CX516 in this test.

The fourth column in the Table shows the MED that produces a statistically significant improvement in behavior in an animal model of depression (MED_D), as described by Malatynska and Kostowski, *Pol.J.Pharmacol.* 40, 357-364 (1984). Compounds 2 and 9 were tested and, again, were much more potent (approximately 500 fold) than the reference compound.

VI. Administration, Dosages, and Formulation

As noted above, the compounds and method of the invention increase AMPA receptor-mediated responses, and are useful for the treatment of hypoglutamatergic conditions. They are also useful for treatment of conditions such as impairment of memory or other cognitive functions, brought on by a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors. They may also be used in the treatment of schizophrenia or schizophreniform behavior resulting from a cortical/striatal imbalance, and in facilitation of learning of behaviors dependent upon AMPA receptors.

Generally, dosages and routes of administration of the compound will be determined according to the size and condition of the subject, according to standard pharmaceutical practices. Dose levels employed can vary widely, and can readily be determined by those of skill in the art. Typically, amounts in the milligram up to gram quantities are employed. The composition may be administered to a subject by various routes, *e.g.* orally, transdermally, perineurally or parenterally, that is, by intravenous, subcutaneous, intraperitoneal, or intramuscular injection. Subjects contemplated for treatment according to the method of the invention include humans, domesticated animals, laboratory animals, and the like.

Formulations containing the compounds of the invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, capsules, powders, sustained-release formulations, solutions, suspensions, emulsions, suppositories, creams, ointments, lotions, aerosols or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

The compositions typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agent, carriers, adjuvants, and the like. Preferably, the composition will be about 0.5% to 75% by weight of a compound or compounds of the invention, with the remainder consisting of suitable pharmaceutical

excipients.. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

Liquid compositions can be prepared by dissolving or dispersing the compounds (about 0.5% to about 20%), and optional pharmaceutical adjuvants, in a carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension. For use in oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form suitable for hydration in water or normal saline.

When the composition is employed in the form of solid preparations for oral administration, the preparations may be tablets, granules, powders, capsules or the like. In a tablet formulation, the composition is typically formulated with additives, *e.g.* an excipient such as a saccharide or cellulose preparation, a binder such as starch paste or methyl cellulose, a filler, a disintegrator, and other additives typically used in the manufacture of medical preparations.

An injectable composition for parenteral administration will typically contain the compound in a suitable i.v. solution, such as sterile physiological salt solution. The composition may also be formulated as a suspension in a lipid or phospholipid, in a liposomal suspension, or in an aqueous emulsion.

Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see "Remington's Pharmaceutical Sciences" (17th Ed., Mack Pub. Co, 1985). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically effective amount for effecting increased AMPA receptor currents in a subject.

EXAMPLES

The following examples illustrate but are not intended in any way to limit the invention.

Unless otherwise stated, all temperatures are given in degrees Celsius. All ¹H NMR spectra were obtained in deuteriochloroform as solvent using tetramethylsilane as an

internal standard. Infrared (IR) spectra were recorded as thin films on a Fresnel crystal in a ATI Mattson Gemini series FTIR.

Note: The distillation of any of the following compounds should be conducted using extreme caution. The danger of release of gaseous decomposition products is exacerbated by increased scale of the reaction. An alternative purification method, using activated charcoal, is described in Example 2, Method B, below.

EXAMPLE 1: 1-(Benzo-2,1,3-thiadiazole-5-ylcarbonyl)piperidine (1)

Trimethylaluminum (2M in toluene; 3.0 mL, 6.0 mmol) was diluted into 30 mL dichloromethane to which piperidine (0.55 g, 6.5 mmol) and methyl benzo-2,1,3-thiadiazole-5-carboxylate (1.16 g, 6.00 mmol) were added. The reaction was stirred at room temperature for 2 hours and concentrated to one-half the volume by rotary evaporation. Dry toluene (25 mL) was added and the reaction solution was heated to 80°C for 1 hour. Additional piperidine (about 0.2 g) was added and the temperature was increased to 100°C for 1 hour. The solution was allowed to cool to room temperature and stirred overnight, at which time it was quenched with 10% citric acid and hydrochloric acid. The solution was diluted with ethyl acetate and sequentially washed with 10% citric acid, saturated sodium hydrogen phosphate and saturated sodium chloride, and subsequently dried over anhydrous sodium sulfate. The solution was concentrated onto silica and product was eluted with hexane/ethyl acetate (3:1). Purification by distillation in a kugelrohr at 180°C and 0.5 mmHg yielded 1-(benzo-2,1,3-thiadiazole-5-ylcarbonyl)piperidine, **1** (1.29 g, 87%) as a pale yellow oil. IR: 2920, 2855, 1633, 1478, 1439, 1280, 1223, 1001, 816, and 748 cm⁻¹. ¹H NMR (500 MHz): δ 8.06 (1H, d, J = 9.1 Hz); 8.02 (1H, s); 7.63 (1H, t, J = 9.0 and 1.5 Hz); 3.77 (2H, br s); 3.40 (2H, br s); 1.72 (4H, br s); and 1.57 ppm (2H, br s).

EXAMPLE 2: 1-(Benzofurazan-5-ylcarbonyl)piperidine (2)

Method A:

Benzofurazan-5-carboxylic acid (2.0 g, 12.2 mmol) was suspended in 10 mL dichloromethane. Carbonyl diimidazole (2.0 g, 12.3 mmol) was added, which caused dissolution with gas evolution. The resulting yellow solution was stirred for 40 minutes at room temperature, following which, piperidine (1.2 g, 14.1 mmol) was added. The solution was stirred overnight and then concentrated onto silica. Product was eluted with hexane/ethyl

acetate (2:1) and purified by distillation in a kugelrohr at 155 - 170°C and 0.5 mmHg. 1-(Benzofurazan-5-ylcarbonyl)piperidine, **2** (2.78 g, 99%), initially a pale yellow oil, crystallized upon cooling. M.p. 88.5-90.5°C. IR: 2938, 2857, 1630, 1519, 1439, 1266, 1223, 996, 881, 816, and 740 cm⁻¹. ¹H NMR (500 MHz): δ 7.90 (1H, d, J = 9.7 Hz); 7.84 (1H, s); 7.44 (1H, dd, J = 9.4 and 1.4 Hz); 3.74 (2H, br s); 3.39 (2H, br s); 1.72 (4H, br s); and 1.57 ppm (2H, br s).

Method B:

A 5-L flask was charged with ethyl acetate (2.3 L) and carbonyl diimidazole (500.0 g, 2.48 mol) to which 4-chloro-3-nitrobenzoic acid (402.5 g, 2.48 mol) was added in portions over 1 hour. The solution was stirred for an additional 1.5 hours. Piperidine (222.2 g, 2.60 mol) was added dropwise over 2 hours and the resulting solution was stirred for an additional 4 hours. The reaction mixture was washed sequentially, twice with 6N HCl solution (600 mL), twice with saturated NaHCO₃ (250 mL), and finally with saturated NaCl (250 mL). The organic solution was dried over anhydrous Na₂SO₄ and filtered, and the solvent was removed *in vacuo* to yield 646 g (97%) of 4-chloro-3-nitrobenzoyl-piperidine as a yellow crystalline solid with m.p. = 76-78 °C. IR: 1633, 1535, and 1440 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.92 (1H, d, J = 1.5 Hz), 7.60 (1H, d, J = 8.1 Hz), 7.56 (1H, dd, J = 8.1 and 1.5 Hz), 3.70 (2H, br s), 3.35 (2H, br s), 1.70 (4H, br s), and 1.56 ppm (2H, br s).

4-Chloro-3-nitro-benzoylpiperidine (539.2 g, 2.00 mol) was dissolved in 2.93 L ethylene glycol in a 5-L flask with stirring and heating to 50 °C. To this solution, sodium azide (137.0 g, 2.10 moles) was added in portions over 40 min. When the addition was complete, the temperature was increased to 120 °C during 2.5 hr and maintained at this temperature for 3 hr. The solution was allowed to cool to 50 °C, at which time additional sodium azide (65.3g, 1.00 moles) was added over 5 min. The temperature was increased to 120 °C during 2.5 hr and maintained at this temperature for 4.5 hr until gas evolution had ceased. The solution was allowed to cool to room temperature, at which time the mixture was partitioned between water and ethyl acetate (1.5 L each). The aqueous phase was extracted three times with ethyl acetate (300 mL). The combined organic phases were washed with 30 mL water, twice with saturated NaCl (200 mL), and finally dried over anhydrous Na₂SO₄. The filtered solution was evaporated to yield 345.5 g of crude 1-(benzofurazan-5-ylcarbonyl)piperidine.

Crude 1-(benzofurazan-5-ylcarbonyl)piperidine (22 g) was dissolved in 200 mL ethyl

acetate with stirring. Activated charcoal (11.0 g) was added to the solution and the resulting suspension was heated to reflux, allowed to cool to 60°C, and finally filtered with the aid of Celite®. The filtered charcoal was re-suspended in 200 mL ethyl acetate, heated to reflux and again filtered with the aid of Celite®. The filter cake was washed twice with ethyl acetate (50 mL) and the filtrate was concentrated on a rotary evaporator to yield 19.0 g orange oil, which solidified upon standing. The decolorized product was washed with 20 mL ice-cold ethanol to yield 13.1 g pale yellow crystals (2) with m.p. = 91.0-93.0 °C.

EXAMPLE 3: 1-(Benzofuroxan-5-ylcarbonyl)piperidine

10 Benzofuroxan-5-carboxylic acid (1 g, 5.6 mmol) was suspended with stirring in 15 mL dichloromethane to which was added carbonyl diimidazole (0.90 g, 5.6 mmol). Gas evolved and the resulting solution was stirred for 40 minutes at which time piperidine (0.5 g, 5.9 mmol) was added with stirring. The reaction solution was concentrated onto silica and product was eluted with hexane/ethyl acetate (3:1). Recrystallization from 2-propanol/hexane
15 (1:10) yielded 1-(benzofuroxan-5-ylcarbonyl)piperidine (0.94 g, 69%) as a yellow solid with m.p. 94.5-96.5°C. IR: 2938, 2855, 1620, 1612, 1528, 1487, 1435, 1257, 1233, 1018, 1000, 852, 811, and 747 cm⁻¹. ¹H NMR (500 MHz): δ 7.10-7.80 (3H, br s); 3.72 (2H br s); 3.39 (2H, br s); 1.72 (4H, br s); and 1.54 ppm (2H, br s).

20 EXAMPLE 4: Preparation of 4-Fluoropiperidine and 1,2,3,6-Tetrahydropyridine

N-Trifluoroacetyl-4-hydroxypiperidine (7.92 g, 40 mmol) was suspended in 10 mL dichloromethane and cooled to -78°C. Diethylaminosulfurtrifluoride (6.8 g, 42 mmol) was added and the suspension was allowed to warm to room temperature overnight. The reaction mixture was then diluted with 125 mL dichloromethane and washed with saturated sodium
25 bicarbonate solution, which resulted in vigorous bubbling. The dichloromethane solution was then dried by washing with a saturated sodium chloride solution followed by treatment with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting orange oil was stirred with a 7.5 M KOH solution for 1h at room temperature. The product was extracted into ether and dried with anhydrous magnesium sulfate. The solution was filtered
30 and the ether was removed by atmospheric distillation. The amines were distilled at 95°C to yield 0.7g colorless oil, which consisted of a mixture of 4-fluoropiperidine/1,2,3,6-tetrahydropyridine. IR: 3317, 3293, 2968, 2955, 2943, 2929, 1451, 1427, 1418, 1377, 1279,

and 1023 cm^{-1} .

EXAMPLE 5: 1-(Benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine (3) and 1-(Benzofurazan-5-ylcarbonyl)-4-fluoropiperidine (4)

5 Benzofurazan-5-carboxylic acid (0.75 g, 4.6 mmol) was suspended in 15 mL dichloromethane. Carbonyl diimidazole (0.75 g, 4.6 mmol) was added to this suspension, which caused the reaction mixture to turn yellow as gas evolved. The solution was stirred for 30 minutes, at which time a mixture of 4-fluoropiperidine and 1,2,3,6-tetrahydropyridine (0.7 g, approximately 7 mmol), prepared as described in Example 4, was added. The
10 solution was stirred for 2 hours at room temperature, at which time the reaction mixture was concentrated onto silica and products were eluted with hexane/ethyl acetate (3:1). Three components were isolated in 100 mg, 200 mg and 300 mg yields. The second eluted compound solidified upon standing and was identified as 1-(benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine, **3** by NMR. M.p. 68.5-70°C. IR: 1630, 1516, 1438, 1245, 1009,
15 881, 816, 741, and 629 cm^{-1} . ^1H NMR (500 MHz): δ 7.92 (1H, d, $J = 9.0$ Hz), 7.88 (1H, s), 7.47 (1H, d, $J = 9.0$ Hz); 5.57-5.95 (2H, m); 4.23 (1H, br s); 3.90-3.97 (2H, m); 3.53 (1H, br s); 2.33 (1H, br s); and 2.22 ppm (1H, br s).

The third eluted component was recrystallized from ethyl acetate/hexane (1:10) to yield 200 mg white crystals with m.p. 124-125.5°C and was identified as 1-(benzofuroxan-5-ylcarbonyl)-4'-fluoropiperidine, **4** by NMR. IR: 1633, 1439, 1274, 1231, 1034, 923, 881, and 742 cm^{-1} . ^1H NMR (500 MHz): δ 7.93 (1H, d, $J = 9.0$ Hz); 7.87 (1H, s); 7.44 (1H, d, $J = 9.0$ Hz); 4.9-5.1 (1H, m); 4.0-4.2 (1H, br s); 3.5-3.7 (2H, m); 3.4-3.5 (1H, br s); 1.7-2.1 ppm (4H, m).

25 EXAMPLE 6: 1-(Benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine (3):

Alternative Method

A more direct route of synthesis of 1-(benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine (**3**) was also performed in a manner similar to Example 2, Method A, above, starting with pure tetrahydropyridine. Crude product (94% yield) was purified by
30 silica gel chromatography (hexane/ethyl acetate; 1:3), which produced a 74% yield of pale yellow crystals with m.p. 82 - 83.5°C; presumably a different crystal isomorph from that obtained above.

EXAMPLE 7: Preparation of 4,4-Difluoropiperidine/1,2,3,6-Tetrahydro-4-fluoropiperidine

N-Trifluoroacetyl-4-piperidone (10 g, 52 mmol) was suspended in 10 mL
dicloromethane. To this suspension, diethylaminosulfurtrifluoride (9.1 g, 56.5 mmol) was
5 added. The reaction proceeded slowly at first but brought the mixture to a rolling boil within
a few minutes. Cooling was applied to moderate the reaction. The mixture was stirred
overnight, diluted with 125 mL dicloromethane and washed with saturated sodium bicar-
bonate solution, upon which vigorous bubbling was observed. The dicloromethane was then
dried with a saturated sodium chloride solution followed by anhydrous magnesium sulfate.
10 The solvent was removed *in vacuo* and the resulting orange oil was stirred with a 7.5 M
KOH solution for 1h at room temperature. The product was extracted into ether, and the
solution was dried with anhydrous magnesium sulfate and filtered. The ether was removed
by atmospheric distillation, and the product was distilled at 105-125°C to yield 4.5 g pale
yellow oil, consisting of a mixture of 4,4-difluoropiperidine/1,2,3,6-tetrahydro-4-fluoro-
15 piperidine. IR: 2960, 1357, 1265, 1146, 1117, 987, 952, 814, and 792 cm⁻¹.

EXAMPLE 8: 1-(Benzofurazan-5-ylcarbonyl)-4,4-difluoropiperidine (5)
and 1-(Benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydro-4-fluoropyridine (6)

Benzofurazan-5-carboxylic acid (0.75 g, 4.6 mmol) was activated in 15 mL
20 dichloromethane with carbonyl diimidazole as above in Example 4. A mixture of 4,4-
difluoropiperidine and 1,2,3,6-tetrahydro-4-fluoropyridine (0.7 g), prepared as described in
Example 7, was added to the solution, which was stirred for 2 hours. The reaction mixture
was concentrated onto silica and product was eluted with hexane/ethyl acetate (3:1) yielding
two components. The first eluted component was recrystallized from ethyl acetate/hexane
25 (1:5) yielding 480 mg of solid with m.p. 148-149°C and was identified as 1-(benzofurazan-5-
ylcarbonyl)-4,4'-difluoropiperidine, 5. IR: 1642, 1440, 1365, 1266, 1123, 1086, 936, 822,
817, 737, 607 cm⁻¹. ¹H NMR (500 MHz): δ 7.96 (1H, d, J = 9.5 Hz); 7.90 (1H, s); 7.45 (1H,
t, J = 8.8 and 1.1 Hz); 3.8-4.1 (2H, br s); 3.5-3.7 (2H, br s); and 1.9-2.2 ppm (4H, br d).

The second eluted component was recrystallized from ethyl acetate/hexane (1:10)
30 yielding 180 mg solid with m.p. 102-105°C and was identified as 1-(benzofurazan-5-
ylcarbonyl)-1,2,3,6-tetrahydro-4-fluoropyridine, 6. IR: 1639, 1436, 1361, 1241, 1146, 1007,
828, 817, 742, 605 cm⁻¹. ¹H NMR (500 MHz): δ 7.94 (1H, d, J = 9.0 Hz); 7.90 (1H, s); 7.46

(1H, d, J = 9.0 Hz); 5.1-5.4 (1H, m); 4.3 (1H, br s); 4.0 (2H, br s); 3.65 (1H, br s); and 2.30-2.55 ppm (2H, br d).

EXAMPLE 9: 4-(Benzofurazan-5-ylcarbonyl)morpholine (7)

5 4-(Benzofurazan-5-ylcarbonyl)morpholine was prepared as described above in Example 2 (Method A), using morpholine in place of piperidine. The product was obtained in 65% yield as a pale crystalline solid with m.p. = 148-150 °C. IR: 1638, 1522, 1439, 1276, 1108, 1003, and 614 cm⁻¹. ¹H NMR (500 MHz): δ 7.94 (1H, d, J = 9.2 Hz), 7.88 (1H, s), 7.45 (1H, d, J = 9.2 Hz), and 3.50-3.90 ppm (8H, m).

10

EXAMPLE 10: 1-(Benzofurazan-5-ylcarbonyl)-4-cyanopiperidine (8)

Method A.

 1-(Benzofurazan-5-ylcarbonyl)-4-carboxamidopiperidine was prepared as above in Example 2 (Method A), using 4-cyanopiperidine in place of piperidine. The product was
15 obtained in 74% yield with m.p. = 190-192 °C following purification by silica gel chromatography with ethyl acetate/methanol (95:5). IR: 1675, 1611, 1431, 1261, and 1226 cm⁻¹. ¹H NMR (200 MHz): δ 7.93 (1H, d, J = 9.2 Hz), 7.88 (1H, s), 7.46 (1H, d, J = 9.1 Hz), 5.30-5.50 (2H, m), 4.60-4.70 (1H, m), 3.75-3.85 (1H, m), 2.90-3.25 (2H, m), 2.40-2.50 (1H, m), and 1.60-2.10 ppm (4H, m).

20 Method B.

 1-(Benzofurazan-5-ylcarbonyl)-4-carboxamidopiperidine (2.50 g, 9.11 mmol) was dissolved in CHCl₃ (90 mL) and treated with thionyl chloride (1.65 g, 13.8 mmol). The reaction mixture was heated to reflux for 30 minutes, at which time the solution appeared turbid. Additional thionyl chloride (1.52 g, 12.8 mmol) was added and the reaction mixture
25 was heated for an additional 1.5 hr. After the solution cooled to room temperature, it was diluted with CH₂Cl₂, washed with saturated NaHCO₃, and dried over Na₂SO₄. The product was concentrated onto silica gel and eluted with hexane/ethyl acetate (1:1). The resulting compound was decolorized with charcoal in ethyl acetate to yield 1-(benzofurazan-5-ylcarbonyl)-4-cyanopiperidine (0.570 g, 24%) (51% based on recovered starting material) as
30 an oil, which crystallized upon standing as a pale solid with m.p. = 104-107°C. IR: 2240, 1735, 1633, 1435, 1271, and 1236 cm⁻¹. ¹H NMR (500 MHz): δ 7.96 (1H, dd, J = 9.0 and 1.2 Hz), 7.88 (1H, dd, 1.7 and 0.7 Hz), 7.44 (1H, dd, J = 9.1 and 1.6 Hz), 3.60-4.0 (4H, m), 2.95-

3.05 (1H, m), and 1.80-2.15 ppm (4H, m).

EXAMPLE 11: 1-(Benzofurazan-5-ylcarbonyl)-4-hydroxypiperidine (9)

1-(Benzofurazan-5-ylcarbonyl)-4-hydroxypiperidine was prepared as described above
5 in Example 2 (Method A), using 4-hydroxypiperidine in place of piperidine. The product
was obtained in 45% yield with m.p. = 132-136 °C following purification by silica gel
chromatography with ethyl acetate. IR: 1614 and 1446 cm⁻¹. ¹H NMR (200 MHz): δ 7.95
(1H, d, J = 9.3 Hz), 7.86 (1H, s), 7.44 (1H, dd, J = 9.2 and 1.3 Hz), 4.0-4.25 (2H, m), 3.1-4.0
(3H, m), 1.8-2.1 (2H, m), and 1.5-1.8 ppm (3H, m). ¹³C NMR (125 MHz): δ 33.6, 34.5, 39.3,
10 44.6, 66.5, 114.6, 117.5, 130.6, 139.1, 148.5, 148.6, and 167.5 ppm.

EXAMPLE 12: 1-(Benzofurazan-5-ylcarbonyl)thiomorpholine (10)

1-(Benzofurazan-5-ylcarbonyl)thiomorpholine was prepared as described above in
Example 2 (Method A), using thiomorpholine in place of piperidine. The product was
15 obtained in 58% yield as a pale crystalline solid with m.p. = 144-146 °C. IR: 2912, 1632,
1557, 1434, 1292, 1231, 1208, 957, 941, 880, 825, 741, and 616 cm⁻¹. ¹H NMR (500 MHz):
δ 7.94 (1H, d, J = 9.6 Hz), 7.86 (1H, s), 7.41 (1H, d, J = 9.2 Hz), 4.06 (2H, br s), 3.73 (2H, br
s), 2.78 (2H, br s), and 2.62 ppm (2H, br s).

20 EXAMPLE 13: 1-(Benzofurazan-5-ylcarbonyl)pyrrolidine (11)

1-(Benzofurazan-5-ylcarbonyl)pyrrolidine was prepared as described above in
Example 2 (Method A), using pyrrolidine in place of piperidine. The product was obtained
in 61% yield as a pale crystalline solid with m.p. = 97.8-99.3 °C. IR: 2957, 2878, 1632,
1619, 1514, 1471, 1432, 1194, 1009, 882, 822, 786, and 742 cm⁻¹. ¹H NMR (500 MHz): δ
25 7.96 (1H, s), 7.91 (1H, d, J = 9.0 Hz), 7.58 (1H, d, J = 9.5 Hz), 3.69 (2H, t, J = 6.6 Hz), 3.50
(2H, t, J = 6.5 Hz), 2.01 (2H, q, J = 6.6 Hz), and 1.96 ppm (2H, t, J = 6.5 Hz).

EXAMPLE 14: 1-(Benzofurazan-5-ylcarbonyl)-3-pyrroline (12)

1-(Benzofurazan-5-ylcarbonyl)-3-pyrroline was prepared as described above in
30 Example 2 (Method A), using 3-pyrroline in place of piperidine. The product was obtained
in 65% yield as a pale crystalline solid with m.p. = 117-118 °C. IR: 3072, 2862, 1633, 1609,
1562, 1535, 1512, 1471, 1460, 1432, 1408, 1360, 1304, 1192, 1156, 1012, 882, 834, 822,

769, 744, 695, 684 cm^{-1} . ^1H NMR (500 MHz): δ 8.00 (1H, s), 7.93 (1H, d, $J = 9.7$ Hz), 7.58 (1H, d, $J = 9.3$ Hz), 5.97 (1H, m), 5.80 (1H, m), 4.50 (2H, s), and 4.30 ppm (2H, s).

EXAMPLE 15: 1-(Benzofurazan-5-ylcarbonyl)-4-methylpiperidine (13)

5 1-(Benzofurazan-5-ylcarbonyl)-4-methylpiperidine was prepared as described above in Example 2 (Method A), using 4-methylpiperidine in place of piperidine. The product was obtained in 67% yield with m.p. = 86-87 °C. IR: 1633, 1441, and 1239 cm^{-1} . ^1H NMR (500 MHz): δ 7.92 (1H, d, $J = 9.5$ Hz), 7.90 (1H, s), 7.44 (1H, d, $J = 9.0$ Hz), 4.50-4.70 (1H, m), 3.65-3.80 (1H, m), 3.05-3.15 (1H, m), 2.80-2.90 (1H, m), 1.75-1.85 (1H, m), 1.60-1.75 (2H, m), 1.20-1.30 (1H, m), 1.05-1.20 (1H, m), and 1.00 ppm (3H, d, $J = 6$ Hz).

EXAMPLE 16: 1-(Benzofurazan-5-ylcarbonyl)hexamethyleneimine (14)

15 1-(Benzofurazan-5-ylcarbonyl)hexamethyleneimine was prepared as described above in Example 2 (Method A), using hexamethyleneimine in place of piperidine. The product was obtained in 67% yield with m.p. = 86-87 °C following purification by silica gel chromatography with hexane/ethyl acetate (1:1). IR: 1631, 1428, 1273, and 743 cm^{-1} . ^1H NMR (500 MHz): δ 7.91 (1H, dd, $J = 8.6, 0.6$ Hz), 7.82 (1H, s), 7.44 (1H, dd, $J = 9.2, 0.8$ Hz), 3.72 (2H, t, $J = 3.9$ Hz), 3.43 (2H, t, $J = 3.9$ Hz), 1.88 (2H, t, $J = 3.9$ Hz), and 1.60-1.70 ppm (6H, m).

EXAMPLE 17: 1-(Benzofurazan-5-ylcarbonyl)-1,4-dioxo-8-azaspiro[4,5]decane (15)

20 1-(Benzofurazan-5-ylcarbonyl)-1,4-dioxo-8-azaspiro[4,5]decane was prepared as described above in Example 2 (Method A), using 1,4-dioxo-8-azaspiro[4,5]decane (the ethylene ketal of 4-pyridone) in place of piperidine. The product was obtained in 54% yield with m.p. = 88-90 °C. IR: 1638, 1440, 1268, 1120, 1081, and 742 cm^{-1} . ^1H NMR (500 MHz): δ 7.91 (1H, dd, $J = 9.0, 1.0$ Hz), 7.87 (1H, dd, $J = 1.6, 0.9$ Hz), 7.45 (1H, dd, $J = 9.2, 1.2$ Hz), 4.00 (4H, s), 3.80-3.95 (2H, br s), 2.45-2.65 (2H, br s), 1.75-1.90 (2H, br s), and 1.65-1.75 ppm (2H, br s).

30 **EXAMPLE 18: 1-(Benzofurazan-5-ylcarbonyl)-4-piperidone (16)**

1-(Benzofurazan-5-ylcarbonyl)-4-piperidone was prepared as described above in Example 2 (Method A), using 4-piperidone in place of piperidine. The product was obtained

in 30% yield with m.p. = 136-139 °C. IR: 1715, 1637, 1433, 1270, and 1238 cm⁻¹. ¹H NMR (500 MHz): δ 7.96 (1H, dd, J = 9.6, 1.0 Hz), 7.94 (1H, s), 7.49 (1H, d, J = 9.6 Hz), 3.70-4.20 (4H, s), and 2.30-2.80 ppm (4H, br s).

5 EXAMPLE 19: 1-(Benzofurazan-5-ylcarbonyl)-4-methoxypiperidine (17)

1-(Benzofurazan-5-ylcarbonyl)-4-hydroxypiperidine (840 mg, 3.40 mmol) was dissolved in dimethylformamide (12 mL) and treated with 60% sodium hydride (150 mg, 3.75 mmol) for 30 minutes. Methyl iodide (650 mg, 4.54 mmol) was added, and, after 3 hours at room temperature, the reaction mixture was further treated with the same quantities
10 of sodium hydride and methyl iodide as above and allowed to stand for 16 hr. The reaction solution was diluted with water and product was extracted into ethyl acetate. The organic solution was washed with water and saturated sodium chloride and dried over MgSO₄. The crude product was purified by decolorization with charcoal in ethanol, twice
15 chromatographed on silica gel by elution with hexane/ethyl acetate (2:1), and finally by kugelrohr distillation at 125-140°C to yield 1-(benzofurazan-5-ylcarbonyl)-4-methoxypiperidine (269 mg, 30%) as a pale yellow oil. IR: 1639, 1440, 1274, 1101, and 1089 cm⁻¹. ¹H NMR (500 MHz): δ 7.91 (1H, dm, J = 9.2 Hz), 7.85 (1H, t, J = 1.1 Hz), 7.43 (1H, dd, J = 9.2 and 1.2 Hz), 3.90-4.05 (1H, m), 3.55-3.72 (2H, m), 3.53 (1H, sept, J = 3.5 Hz), 3.38 (3H, s), 3.20-3.35 (1H, m), 1.90-2.02 (1H, m), 1.65-1.85 (2H, m), and -1.65 ppm
20 (1H, m).

EXAMPLE 20: 1-(Benzofurazan-5-ylcarbonyl)decadeuteropiperidine (18)

Benzofurazan-5-carboxylic acid (0.9070 g, 5.526 mmol) was suspended in 15 mL methylene chloride. To this solution, carbonyl diimidazole (0.9027g, 5.567 mmol) was
25 added. The reaction mixture turned dark as gas evolved. The solution was stirred for 30 minutes, at which time piperidine-d¹¹ (0.5125 g, 5.437 mmol) was added. The reaction mixture was stirred for two hours at room temperature, concentrated onto silica gel, and eluted with hexane/ethyl acetate (2:1) to yield 1-(benzofurazan-5-ylcarbonyl)decadeutero-
30 piperidine (911.1 mg, 69%) as a pale crystalline solid with m.p. = 88-89 °C. IR: 2213, 2113, 1624, 1517, 1416, 1233, 1103, 970, 930, 897, 881, 872, 772, 740, and 605 cm⁻¹. ¹H NMR (500 MHz): δ 7.91 (1H, d, J = 9.8 Hz), 7.84 (1H, s), and 7.44 ppm (1H, dd, J = 9.4 and 1.4 Hz).

EXAMPLE 21: *In Vitro* Physiological Testing

The physiological effects of invention compounds were tested *in vitro* with slices of rat hippocampus according to the following procedure. Excitatory responses (field EPSPs) were measured in hippocampal slices, which were maintained in a recording chamber continuously perfused with artificial cerebrospinal fluid (ACSF). During a 15 - 30 minute interval, the perfusion medium was switched to one containing various concentrations of the test compounds. Responses collected immediately before and at the end of drug perfusion were superimposed in order to calculate the percent increase in EPSP amplitude.

To conduct these tests, the hippocampus was removed from anesthetized, 2 month old Sprague-Dawley rats and *in vitro* slices (400 micrometers thick) were prepared and maintained in an interface chamber at 35 °C using conventional techniques [see, for example, Dunwiddie and Lynch, *J. Physiol.* 276: 353-367 (1978)]. The chamber was constantly perfused at 0.5 mL/min with ACSF containing (in mM): NaCl 124, KCl 3, KH₂PO₄ 1.25, MgSO₄ 2.5, CaCl₂ 3.4, NaHCO₃ 26, glucose 10 and L-ascorbate 2. A bipolar nichrome stimulating electrode was positioned in the dendritic layer (stratum radiatum) of the hippocampal subfield CA1 close to the border of subfield CA3.

Current pulses (0.1 msec) through the stimulating electrode activate a population of the Schaffer-commissural (SC) fibers which arise from neurons in the subdivision CA3 and terminate in synapses on the dendrites of CA1 neurons. Activation of these synapses causes them to release the transmitter glutamate. Glutamate binds to the post-synaptic AMPA receptors which then transiently open an associated ion channel and permit a sodium current to enter the postsynaptic cell. This current results in a voltage in the extracellular space (the field EPSP) which is recorded by a high impedance recording electrode positioned in the middle of the stratum radiatum of CA1.

For the experiments summarized the table, the intensity of the stimulation current was adjusted to produce half-maximal EPSPs (typically about 1.5 - 2.0 mV). Paired stimulation pulses were given every 40 sec with an interpulse interval of 200 msec (see below). The field EPSPs of the second response were digitized and analyzed to determine amplitude. If the responses were stable for 15-30 minutes (baseline), test compounds were added to the perfusion lines for a period of about 15 minutes. The perfusion was then changed back to regular ACSF.

Paired-pulse stimulation was used since stimulation of the SC fibers, in part, activates interneurons which generate an inhibitory postsynaptic potential (IPSP) in the pyramidal cells of CA1. This feed forward IPSP typically sets in after the EPSP reaches its peak. It accelerates the repolarization and shortens the decay phase of the EPSP, and thus could partially mask the effects of the test compounds. One of the relevant features of the feed-forward IPSP is that it can not be reactivated for several hundred milliseconds following a stimulation pulse. This phenomenon can be employed to advantage to eliminate IPSP by delivering paired pulses separated by 200 milliseconds and using the second ("primed") response for data analysis.

The first data column of Table I shows the estimate of the concentration of each test compound that would be required to increase the amplitude of the field EPSP to a value 10% above the baseline level. Values were estimated by interpolation in most cases, but by extrapolation from determined values for others.

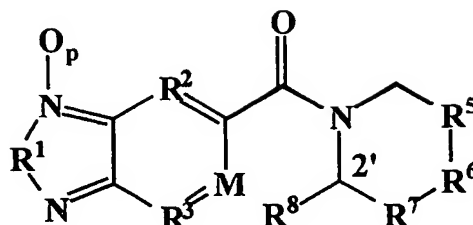
EXAMPLE 22: Behavioral Testing

The second data column in Table 1 shows the Minimum Effective Dose (MED₅) for activity in a methamphetamine/rat model for assessing the probable efficacy of neuroleptic drugs for the treatment of schizophrenia (Larson *et al.*, *Brain Res.*, *supra*). The dose recorded is that which reduced the hyperactivity and/or the stereotypic activity induced by acute administration of 2 mg/kg methamphetamine in Sprague-Dawley rats aged 2-4 months. Activity was monitored for 90 minutes using two rows of multiple, paired infrared diode-detectors such that the lower row detected locomotion and the upper row detected rearing behavior. Data were collected by and stored in a personal computer for later analysis.

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications may be made without departing from the invention.

IT IS CLAIMED:

1. A compound having the structure:



in which:

R¹ is oxygen or sulfur;

R² and R³ are independently selected from the group consisting of -N=, -CR=, and

10 -CX=;

M is =N- or =CR⁴-, wherein R⁴ and R⁸ are independently R or together form a single linking moiety linking M to the ring vertex 2', the linking moiety being selected from the group consisting of a single bond, -CRR'-, -CR=CR'-, -C(O)-, -O-, -S(O)_y-, -NR-, and -N=; and

15 R⁵ and R⁷ are independently selected from the group consisting of -(CRR')_n-, -C(O)-, -CR=CR'-, -CR=CX-, -CRX-, -CXX'-, -S-, and -O-, and

R⁶ is selected from the group consisting of -(CRR')_m-, -C(O)-, -CR=CR'-, -CRX-, -CXX'-, -S-, and -O-;

wherein

20 X and X' are independently selected from -Br, -Cl, -F, -CN, -NO₂, -OR, -SR, -NRR', -C(O)R, -CO₂R, or -CONRR', wherein two groups R or R' on an individual group X, or on two adjacent groups X, may together form a ring; and

R and R' are independently selected from (i) hydrogen, (ii) C₁-C₆ branched or unbranched alkyl, which may be unsubstituted or substituted with one or more

25 functionalities selected from halogen, nitro, alkoxy, hydroxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide, and wherein two such alkyl groups on a single carbon or on adjacent carbons may together form a ring, and (iii) aryl, which may be unsubstituted or substituted with one or more functionalities selected from

halogen, nitro, alkoxy, hydroxy, aryloxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide;

m and p are, independently, 0 or 1; and

n and y are, independently, 0, 1 or 2.

5

2. A compound in accordance with claim 1 in which R and R' are independently selected from (i) hydrogen and (ii) C₁-C₆ branched or unbranched alkyl, which may be unsubstituted or substituted with one or more functionalities selected from halogen, nitro, alkoxy, hydroxy, alkylthio, amino, keto, aldehyde, carboxylic acid, carboxylic ester, or carboxylic amide, and
10 wherein two such alkyl groups on a single carbon or on adjacent carbons may together form a ring.

3. A compound in accordance with claim 1 in which R² and R³ are -CR- and M is =CR⁴-.

- 15 4. A compound in accordance with claim 3 in which p is 0, R¹ is oxygen, and R⁴ and R⁸ are hydrogen.

5. A compound in accordance with claim 4 in which R⁵ and R⁷ are -(CRR')_n- and R⁶ is -(CRR')_m-.

20

6. A compound in accordance with claim 5 in which R and R' are hydrogen and m = n = 1, said compound being 1-(benzofurazan-5-ylcarbonyl) piperidine.

7. A compound in accordance with claim 3 in which p is 0, R¹ is sulfur, R⁴, R⁸, R, and R'
25 are hydrogen, and m = n = 1, said compound being 1-(benzo-2,1,3-thiadiazole-5-ylcarbonyl)piperidine.

8. A compound in accordance with claim 4 in which R⁵ is -CR=CX-, R⁶ is -(CRR')_m-, R⁷ is -(CRR')_n-, and m is 0.

30

9. A compound in accordance with claim 8 in which R and R' are hydrogen.

10. A compound in accordance with claim 9 in which X is fluorine and n is 1, said compound being 1-(benzofurazan-5-ylcarbonyl)-4-fluoro-1,2,3,6-tetrahydropyridine.
11. A compound in accordance with claim 4 in which R^5 is $-CR=CR'$ -, R^6 is $-(CRR')_m$ -, R^7 is $-(CRR')_n$ -, and m is 0.
12. A compound in accordance with claim 11 in which R and R' are hydrogen.
13. A compound in accordance with claim 12 in which n is 1, said compound being 1-(benzofurazan-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine.
14. A compound in accordance with claim 4 in which R^5 and R^7 are $-(CRR')_n$ -, and R^6 is $-C(O)$ -, $-CRX$ -, CXX' -, $-O$ -, or $-S$ -.
15. A compound in accordance with claim 14 in which R^6 is $-CXX'$ -, R and R' are hydrogen, n is 1, and X is fluorine, said compound being 1-(benzofurazan-5-ylcarbonyl)-4',4'-difluoropiperidine.
16. A compound in accordance with claim 14 in which R^6 is $-CRX'$ -, R and R' are hydrogen, and n is 1.
17. A compound in accordance with claim 16, wherein said compound is selected from 1-(benzofurazan-5-ylcarbonyl)-4'-fluoropiperidine, 1-(benzofurazan-5-ylcarbonyl)-4'-cyano-piperidine, and 1-(benzofurazan-5-ylcarbonyl)-4'-hydroxypiperidine.
18. A compound in accordance with claim 14 in which R^6 is $-O$ -, $-S$ -, or $-C(O)$ -, n is 1, and R and R' are hydrogen, said compound being selected from 4-(benzofurazan-5-ylcarbonyl)morpholine, 4-(benzofurazan-5-ylcarbonyl)thiomorpholine, and 4-(benzofurazan-5-ylcarbonyl)-4-piperidone.
19. A compound in accordance with claim 1 in which M is $=CR^4$ -, wherein R^4 and R^8 together form a single linking moiety linking M to the ring vertex 2', the linking moiety

being a single bond, -CRR'-, -CR=CR'-, -C(O)-, -O-, -S-, -NR-, or -N=.

20. A compound in accordance with claim 19 in which R² and R³ are -CR=.

5 21. A compound in accordance with claim 20 in which p is 0, R¹ is oxygen, R⁵ and R⁷ are -(CRR')_n-, and R⁶ is -(CRR')_m-.

22. A compound in accordance with claim 21 in which n = 1.

10 23. A compound in accordance with claim 21 in which the linking moiety is -CRR'-, -O-, -S-, or -N=.

24. A compound in accordance with claim 23 in which the linking moiety is -O-.

15 25. Use of a compound in accordance with any of claims 1 to 24, in a pharmaceutically acceptable carrier, for enhancing AMPA receptor function in a mammalian subject.

26. Use of a compound as in claim 25, wherein said enhancing is effective to alleviate impairment of memory or other cognitive functions, such as is caused by a hypoglutamatergic condition or by deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors.

20

27. Use of a compound as in claim 25, wherein said enhancing is effective to treat schizophrenia or schizophreniform behavior resulting from a cortical/striatal imbalance, such as is caused by a hypoglutamatergic condition or by deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors.

25

28. Use of a compound as in claim 25, wherein said enhancing is effective to facilitate learning of behaviors dependent on AMPA receptor functioning.

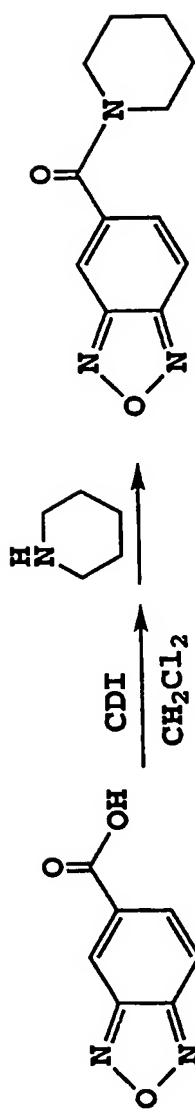
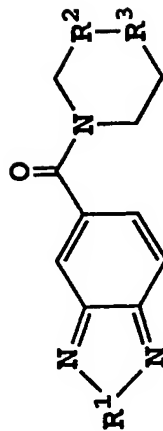
30

29. Use of a compound as in claim 25, in which said compound is in accordance with any of claims 2 to 18.

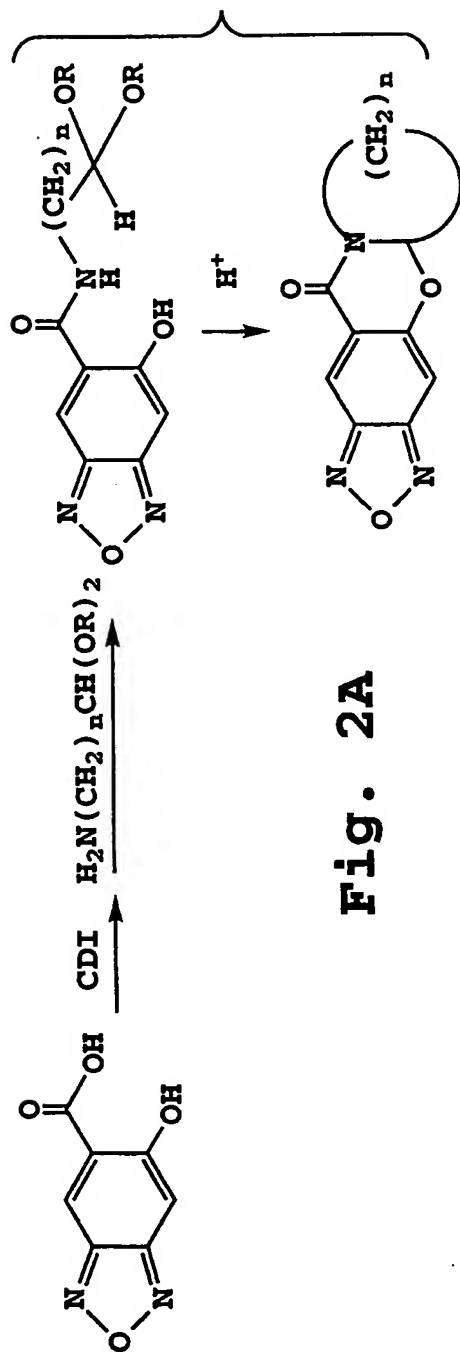
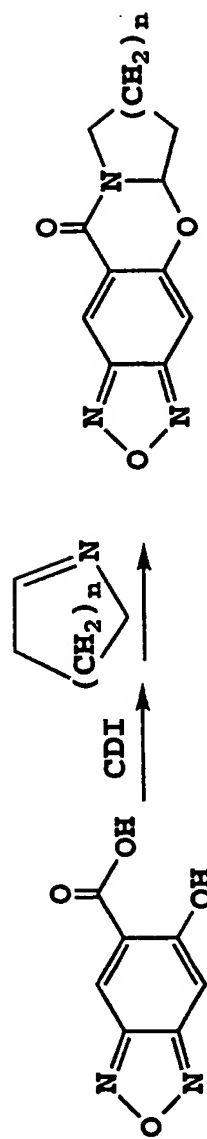
30. Use of a compound as in claim 26, in which said compound is selected from the group consisting of:

- a. 1-(benzofurazan-5-ylcarbonyl) piperidine,
- b. 1-(benzo-2,1,3-thiadiazole-5-ylcarbonyl)piperidine,
- 5 c. 1-(benzofurazan-5-ylcarbonyl)-4-fluoro-1,2,3,6-tetrahydropyridine,
- d. 1-(benzofurazan-5-ylcarbonyl)-4'-fluoropiperidine,
- e. 1-(benzofurazan-5-ylcarbonyl)-4',4'-difluoropiperidine,
- f. 1-(benzofurazan-5-ylcarbonyl)-4'-cyanopiperidine,
- g. 1-(benzofurazan-5-ylcarbonyl)-4'-hydroxypiperidine,
- 10 h. 4-(benzofurazan-5-ylcarbonyl)morpholine,
- i. 4-(benzofurazan-5-ylcarbonyl)thiomorpholine, and
- j. 4-(benzofurazan-5-ylcarbonyl)-4-piperidone.

1/3

**Fig. 1****Fig. 3**

2/3

**Fig. 2A****Fig. 2B**

3/3

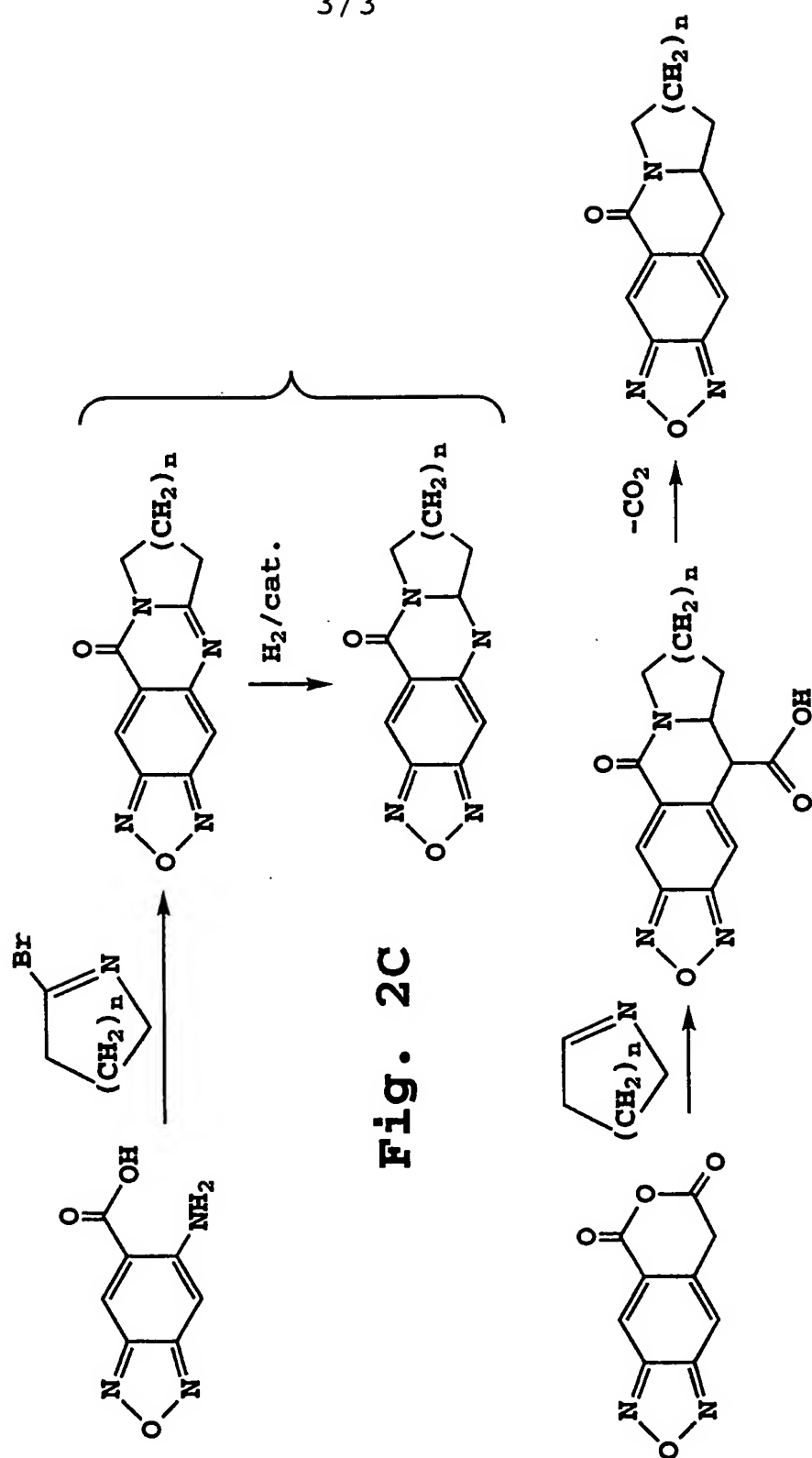


Fig. 2D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/02713

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D285/14 A61K31/445 C07D271/12 C07D413/06 A61K31/535
C07D417/06 A61K31/54 C07D498/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 02475 A (UNIV CALIFORNIA ; LYNCH GARY S (US); ROGERS GARY A (US)) 3 February 1994 cited in the application see page 36; claim 1; example XII	1-30
P, A	WO 97 36907 A (UNIV CALIFORNIA ; CORTEX PHARMA INC (US)) 9 October 1997 cited in the application see claim 1	1-30
A	EP 0 709 384 A (MERCK PATENT GMBH) 1 May 1996	1-30
A	US 3 981 864 A (TANAKA SATORU ET AL) 21 September 1976 see claim 1	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 May 1998

Date of mailing of the international search report

05/06/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/02713

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9402475	A	03-02-1994	AU 4781593 A CA 2138533 A EP 0651746 A JP 7509468 T	14-02-1994 03-02-1994 10-05-1995 19-10-1995
WO 9736907	A	09-10-1997	US 5736543 A AU 2427497 A	07-04-1998 22-10-1997
EP 0709384	A	01-05-1996	DE 4438810 A DE 19526269 A AU 3443595 A CA 2161618 A CN 1128762 A CZ 9502816 A FI 955184 A HU 76068 A JP 8225569 A NO 954349 A PL 311185 A SK 135595 A US 5698553 A ZA 9509170 A	02-05-1996 23-01-1997 09-05-1996 01-05-1996 14-08-1996 15-05-1996 01-05-1996 30-06-1997 03-09-1996 02-05-1996 13-05-1996 05-06-1996 16-12-1997 27-05-1996
US 3981864	A	21-09-1976	JP 1231979 C JP 50050387 A JP 59006877 B JP 1203165 C JP 50050388 A JP 58035194 B DE 2442750 A FR 2242978 A GB 1484291 A US 4026895 A US 4051125 A US 4083853 A US 4117228 A	26-09-1984 06-05-1975 15-02-1984 25-04-1984 06-05-1975 01-08-1983 13-03-1975 04-04-1975 01-09-1977 31-05-1977 27-09-1977 11-04-1978 26-09-1978